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10/566,432	09/19/2006	Mohamed A. Marahiel	12180-0002	5768

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CLARK & BRODY
1700 Diagonal Road, Suite 510
Alexandria, VA 22314

EXAMINER	
FERNANDEZ, SUSAN EMILY	
ART UNIT	PAPER NUMBER
1651	
MAIL DATE	DELIVERY MODE
11/29/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,432	MARAHIEL ET AL.	
	Examiner	Art Unit	
	SUSAN E. FERNANDEZ	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2009 and 01 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *6-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,15 and 16* is/are rejected.

7)☒ Claim(s) *2-5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/19/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The responses filed July 31, 2009, and June 1, 2010, have been received and entered.

Claims 1-16 are pending.

Election/Restrictions

Applicant's election with traverse of the invention of Group I and the species (S for group A, H for each of R1, R2, R3, R4, and R5, alkyl for Group L, and claim 5) in the replies filed on July 31, 2009 and June 1, 2010, is acknowledged. The traversal is on the ground(s) that the applicant asserts that the single common technical feature found in claims 1 and 10 was mischaracterized. The applicant asserts that the charge stabilizing leaving group is the single common technical feature of the invention. This is not found persuasive because it is not clear that the charge stabilizing leaving groups of claims 1 and 10 are the same. Unlike claim 1, claim 10 does not require that the charge stabilizing leaving group is bound to the acyl residue of the resulting linear peptide of claim 10. It is also not clear that there is a common structure present.

The requirement is still deemed proper and is therefore made FINAL.

Claims 6-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and nonelected species, there being no allowable generic or linking claim.

Claims 1-5, 15, and 16 are examined on the merits to the extent they read on the elected subject matter.

Claim Objections

Claims 2-5 are objected to because of the following informalities:

Claims 2-5 should begin with the recitation "The method..."

Claim 3 is objected to because NRPS and PKS should be defined in parentheses as "non-ribosomal peptide synthetase" and "polyketide synthase."

Claim 5 is also objected to because the sixth line from the bottom recites "heterocyclic groups stand" which should be replaced with "heterocyclic group stands." Furthermore, the word "and" should be inserted before "phosphorus" in the seventh and fourth lines from the bottom, and in the last line.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 15 and 16 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 5, 15, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 3, the phrase "preferably" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 5 is indefinite since it is not clear that A is selected from O and S, or that R1-R5 are each selected from the species written after "and whereby R1, R2, R3, R4, and R5 are independent of one another:". Similarly, it is not clear that L is selected from the species written after "L =." Claim 5 should clearly define that A, R1-R5, and L are selected from the group of species which follow the ":" and "=" signs.

Claims 15 and 16 provide for the use of cyclic peptides and charge-stabilized leaving groups, respectively, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 15, and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods involving a nucleophilic leaving group that has a thiol, does not reasonably provide enablement for any and all nucleophilic leaving groups. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Regarding undue experimentation, *In re Wands*, 8 USPQ2d 1400, at 1404 (Fed. Cir. 1988) states:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. (Citations omitted).

Specifically, there is a lack of working examples of the production of cyclic peptides according to the claimed process wherein the leaving group is other than leaving groups with a thiol. Embodiments 1-3 on pages 28-29 teach thiophenol or benzylmercaptane leaving groups, which each have a thiol. Furthermore, thiocresole and methoxythiophenol are also taught as leaving groups (page 33, lines 9-32), wherein each of the leaving groups also have a thiol. There is a clear absence of working examples involving leaving groups also than these thiol-containing compounds.

Additionally, a large quantity of experimentation would be required to ensure that any of the numerous possible nucleophilic leaving groups would have activated the acyl residue of the linear peptide, and that cyclization would have occurred. There is a great amount of unpredictability of the art as it was previously found that various peptide cyclases were found to be inactive with peptidyl SNAC substrates (Sieber, Angew. Chem. 2004. 43: 493-498). Because

of the lack of working examples, the large quantity of experimentation that would be required, and the unpredictability of the art, undue experimentation would be required and thus does not enable the practice of the invention wherein the leaving group does not have a thiol.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3, 4, 15, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Walsh (US 2002/0192773. Listed on 9/19/06 IDS).

Walsh discloses a method of preparing macrocyclic molecules from linear substrates wherein ring-closure of the linear substrates is "...effected preferably by the formation of an amide or an ester bond catalyzed by a thioesterase domain excised and expressed from the DNA sequence for non-ribosomal peptide synthetase (NRPS) or polyketide synthase (PKS) multidomain proteins" (page 2, paragraph [0013]). More specifically, the purified excised thioesterase (TE) domain protein is brought in contact with the linear substrate which comprises a compound having an activated acyl residue such that a TE-O-acyl bond forms (page 2, paragraph [0015]). Therefore, the activated acyl residue of the linear substrate selectively acylates the TE domain protein.

Walsh teaches that the linear substrate can be of Formula (III) with a linear backbone of at least 14 atoms connected to the thioester having an R group that is a lower alkyl group which can be substituted (page 3, paragraphs [0033]-[0036]). The excised TE domain protein catalyzes the cyclization of the substrate of Formula (III) to a cyclic product of Formula (IV) (page 3, paragraphs [0037]-[0040]). See also page 2, paragraphs [0021]-[0027], showing the macrocyclization of a linear substrate of Formula (I) to the macrocyclic molecule of Formula (II). It is noted that SR of Formula (I) can be N-acetylcysteamine, SNAC (page 7, paragraph [0092]), which is considered to be the substrate leaving group (claim 15). It is also apparent from Formulas (I)-(IV), as well as Figure 1(b), that SR is a leaving group that is cleaved off during formation of the macrocylic molecules. Furthermore, given the formulas, it is also apparent that SR is a charge-stabilized leaving group chemically bound to the acyl group of the C-terminal carboxylic acid group of the linear substrate (see also page 3, paragraph [0042] which recites a "C-terminal thioester activated acyl group").

The linear substrate of the invention can comprise both synthetic and biosynthetic amino acid residues (page 3, paragraph [0042]). For example, the linear substrate can comprise depsipeptides or a variable number of amino acid residues (page 3, paragraph [0032]). Therefore, the linear substrate can be a linear peptide, and the resulting macrocylic molecule can be a cyclic peptide. For instance, see Example 3, Examples 4-17, and Table 1 on page 13, wherein various peptide-SNAC substrates were created and incubated with TE according to the Walsh process to form tyrocidine A and related macrocyclic peptides. Therefore, it is clear that instant claims 1, 4, and 16 are anticipated by Walsh.

Furthermore, the excised TE domain protein are isolated and purified, and are from multidomain NRPS or PKS (page 4, paragraph [0046]). Therefore, instant claim 3 is anticipated. Also, the macrocyclic molecules prepared by the Walsh process can have useful pharmaceutical applications, including use as antibiotics, antitumor agents, cholesterol-lowering drugs, and immunosuppressants (page 12, paragraph [0197]). Thus, instant claim 15 is anticipated by the reference.

A holding of anticipation is clearly required.

Claims 1-5 and 16 are rejected under 35 U.S.C. 102(a) as being anticipated by Grunewald (Biochemistry. 2004. 43: 2915-2925. Published on web 2/20/04. Listed on 9/19/06 IDS).

Grunewald teaches the use of the thioesterase (TE) domain of CDA non-ribosomal peptide synthetase (page 2915, last paragraph and page 2916, first two full paragraphs). CDA is calcium-dependent antibiotic which has a macrocyclic structure (page 2915, first paragraph). A CDA3 TE domain was cloned, expressed and purified (page 2916, last paragraph through page 2917, first paragraph). Various linear peptides, including peptidyl thiophenol substrates, were created (page 2917, first column, first two full paragraphs) and treated with the recombinant CDA3 cyclase which catalyzed ring formation of the substrates (abstract). Figure 10 demonstrates the acylation of the CDA3 cyclase with the 1-thiophenol substrate (page 224), wherein "1" of 1-thiophenol is peptide sequence shown in Figure 4 on page 220. As shown in Figure 10, the active site serine residue of the CDA3 cyclase is acylated by the reactive 1-thiophenol substrate, and the thiophenol group is cleaved off, serving as a charge-stabilized leaving group bound to the acyl group of the C-terminal carboxylic acid group of the substrate.

From the reaction, a cyclic peptide is formed (a decapetide lactone or an undecapeptide lactone). Clearly from Figure 10 and the discussion above, it is apparent that instant claims 1, 2 (charge-stabilized leaving group is thiophenol), 3, 4, 5 (charge-stabilized leaving group is thiophenol), and 16 are anticipated by Grunewald.

A holding of anticipation is clearly required.

Claims 1-5 and 16 are rejected under 35 U.S.C. 102(a) as being anticipated by Sieber (Angew. Chem. 2004. 43: 493-498. Published online January 14, 2004).

Sieber discloses a method for creating cyclic compounds through activity-based TE (thioesterase) enzyme acylation with reactive thioester leaving groups (thiophenol) (page 499, second column, first full paragraph). The TE domain is a domain in a nonribosomal peptide synthetase (NRPS) (page 499, first paragraph). For one portion of the study, a fengycin peptide cyclase was created as biodomainal fragment ppan-PCP-TE (page 499, second column), and fengycin thiophenol was synthesized in order to observe a thioester exchange reaction between the enzyme and the fengycin thiophenol (page 499, second column, last paragraph). Scheme 2 on page 500 shows the activity-based enzyme acylation, wherein the active-site serine residue of the fengycin peptide cyclase (TE) was selectively acylated by the reactive peptidyl thiophenol substrate to result in the creation of cyclic peptidolactone fengycin. It is clear from Scheme 2 that the thiophenol leaving group is a charge-stabilized group chemically bound to the acyl group of the C-terminal carboxylic acid group of the linear peptide (fengycin), and that a cyclic peptide with a ring of at least 5 atoms was formed. Thus, instant claims 1, 2 (thiophenol), 3, 4, 5 (thiophenol), and 16 are anticipated by Sieber.

A holding of anticipation is clearly required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 15, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grunewald.

As discussed above, Grunewald anticipates claims 1-5 and 16. However, it does not expressly disclose that the cyclic products (the decapeptide lactone or the undecapeptide lactone) obtained by use of the recombinat CDA3 cyclase are used for the production of a pharmaceutical for the therapy, diagnosis and prophylaxis of diseases in which bacterial infections occur. However, Grunewald indicates that "Macrocyclization represents an important pathway in nature

to obtain highly bioactive compounds with important pharmaceutical applications" wherein such compounds obtained include antibiotics such as CDA (page 2915, first paragraph). Moreover, Grunewald points to previous research that found that generated comprehensive libraries of new macrocyclic comounds which were screened for improved therapeutic activity (page 2915, second column, first paragraph). Therefore, at the time the invention was made, it would have been obvious to the person of ordinary skill in the art to have used the Grunewald method of catalyzing ring formation of linear peptidyl thioester substrates (including those with thiophenol leaving groups) to generate macrocyclic products for use as antibiotics or as other therapeutics. One of ordinary skill in the art would have been motivated to do this as macrocyclic compounds had been recognized and screened for their therapeutic activities, and had been used as antibiotics. Furthermore, in experiments conducted by Grunewald, the linear peptidyl thioester substrates used were based on a sequence analogous to natural CDA (abstract). Therefore, by catalyzing the ring formation of these linear substrates, it would appear that the resulting cyclic peptides would have had properties similar to natural CDA, including the therapeutic properties. In sum, claim 15 is rendered obvious.

A holding of obviousness is clearly required.

Claims 1-5, 15, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sieber.

As discussed above, Sieber anticipates claims 1-5 and 16. However, it does not expressly disclose that the cyclic compounds obtained through activity-based TE enzyme acylation with reactive thioester leaving groups (thiophenol) are used for the production of a pharmaceutical for

the therapy, diagnosis and prophylaxis of diseases in which bacterial infections occur. However, Sieber indicates that the common feature of various natural small peptide molecules having exceptional pharmacological and biological activities, which include antibiotics, is their rigidity which is often achieved by cyclization of the peptide backbone (page 499, first paragraph). Therefore, researchers have sought to produce modified natural cyclic peptides by different mechanisms (page 499, first paragraph). Given that it is recognized that peptide cyclization can produce cyclic peptides with pharmacological and biological activities, it would have been obvious to have used the method of Sieber to produce cyclic peptides for use as therapeutics, including as use as antibiotics. Moreover, the product produced in Scheme 2 of Sieber, fengycin, is a known antibiotic. Therefore, instant claim 15 is rendered obvious.

A holding of obviousness is clearly required.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUSAN E. FERNANDEZ whose telephone number is (571)272-3444. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Primary Examiner, Art Unit 1651

Susan E. Fernandez
Examiner
Art Unit 1651

sef